REMARKS

I. Status of the Claims

Claims 1-82 are pending in the instant application. Claims 1-20 and 28-82 were withdrawn form consideration as being directed to non-elected subjected matter pursuant to a restriction requirement. Claims 21-27 were examined in the instant Office Action and stand variously rejected under 35 U.S.C. §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the invention, 35 U.S.C. §112 first paragraph, for lack of enablement, and under 35 U.S.C. §102(b)/103. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

The claims presented herein by way of amendment are fully supported by the specification as filed, and entry of the instant amendment does not constitute and introduction of new matter in the specification. Merely by way of example, support for the new claims 83-95 may be found generally in the specification in Table 6 located at page 30, and in the original claims. The following table also indicates the locations in the specification where support for claim 96-101 may be found. The locations listed in following table are only ***exemplary*** of the support that can be found and additional explicit support for the substrates also is present elsewhere throughout the specification.

Claim	Support in the Specification
96	SEQ ID NO:152 of sequence listing; page 13, lines 10-12; Table 5 at page 25, page 25, lines 26-29.
97	SEQ ID NO:158 of sequence listing; page 6, line 27; page 26, lines 19-20.
98	SEQ ID NO:153 of sequence listing; Table 5 at page 25.
99	SEQ ID NO:191 of sequence listing; page 26, line 20
100	SEQ ID NO:151 of sequence listing; Table 5 at page 25.
101	SEQ ID NO:149 of sequence listing; Table 5 at page 25.

II. Renewed request for reconsideration of restriction requirement.

Applicants have previously requested reconsideration of the restriction requirement. Applicants thank the Examiner for the additional comments provided in response to that request. Applicants will petition the restriction requirement pursuant to the provisions of 37 C.F.R. §1.144. In order to preserve rights to file such a petition, Applicants renew the request for reconsideration for reasons previously of record. In the meantime, Applicants have amended the claims to be directed to subject matter in which P_1 is defined as Y.

III. Rejection under 35 U.S.C. §112, second paragraph should be withdrawn

Claim 26 was rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. More specifically, the Examiner pointed out that the word "bind" in line 3 of the claim should be "bond" and the term ""P_1--P_1" in lines 3 and 4 of the claim should be "P_1--P_1'." Applicants thank the Examiner for pointing out these typographical errors and have amended the claim in accordance with the Examiner's suggestions at page 3 of the Office Action.

IV. Rejection under 35 U.S.C. §112, first paragraph should be withdrawn

Claims 21-27 were rejected under 35 U.S.C. §112, first paragraph as supposedly containing subject matter which was not described in such a way as to enable one of skill in the art to make and use the invention. Applicants respectfully traverse.

In the Office Action the Examiner asserted that the claims of the invention were drawn to "millions upon millions of embodiments" and that given this "extremely large number," Applicants "have not enabled the making and/or using of all of the embodiments of the instant claims." The Examiner further states that "[w]hether or not a particular peptide sequence will be cleaved by the protein encoded by SEQ ID NO:1 or 3 cannot be ascertained by the office and would require obtaining the peptide and testing it with the two proteases. The office does not have facilities to do such testing and must rely upon applicants to do this." Applicants respectfully traverse the rejection, firstly because the specification as filed in fact does teach how one of skill how to make and use the claimed peptides and secondly, because the Examiner appears to be applying an erroneous legal standard for determining whether a specification

provides the requisite teachings to conform with the statutory requirements of 35 U.S.C. §112, first paragraph.

The application as filed teaches there is a need "to identify compounds that may act as surrogates for the APP substrate of Hu-Asp2." (Specification, page 3, lines 16-18). In order to address this need, the inventors designed novel Hu-Asp2 substrates and conducted comparisons of these novel compounds with "known Hu-Asp2 substrates to elucidated information regarding specific amino acid occupancy at and around the cleavage site." (Specification, page 16, lines 12-15). From these comparisons, the inventors discovered that the peptide substrates that were most "effective Hu-Asp2 substrates, Tyr/Phe and Leu were the most abundant amino acids at the P_1 site; Asn appeared several times at the P_2 site; Glu, Asp, and Ala, were prominent in the P_1'; Val occurred frequently in the P_2'; the sequence Glu-Val-Glu appeared at the P_1' P_2' P_3' of ubiquitin, another Asp2 substrate." (Specification, page 19, lines 8-14). Using these observations, the inventors designed exemplary peptides such as those presented in Table 2. (Specification page 20). In addition, the specification provides explicit teachings of optimization of the peptides to "produce minimally altered APP forms that are highly susceptible to □- secretase cleavage." (Specification, page 23, lines 1-3). In doing so, the inventors "produced substrates superior to the Swedish mutation peptide (with respect to β-secretase cleavage) by changing the four amino acids ...NL-□- DA...(SEQ ID NO:142) which encompass the □- secretase cleavage site in APP Swedish mutation to ...SY-□- EV....(SEQ ID NO:141)." (Specification, page 23, lines 16-22).

The enablement requirement of 35 U.S.C. §112, first paragraph requires only that the specification provides a teaching of how one of skill in the art could make the invention and how one of skill in the art should use the claimed invention. The above recitations from the specification exemplify that that the specification explicitly teaches one skilled in the art how to produce peptides comprising specific sequences as artificial substrates for Hu-Asp2. In addition, the specification also provides express guidance of methods of producing such peptides using either conventional automated peptide synthesis techniques or recombinant technologies. (see Section IV of Specification, pages 42-52). That section of the specification also provides detailed descriptions of exemplary peptide purification techniques. Therefore, at this stage, the

teachings of the specification have taught the skilled artisan how to make peptides of the scope of the invention.

Additionally, the specification also teaches those of skill in the art how to use the claimed invention. For example, the specification at page 41, lines 14-23 teaches exemplary experimental assay protocol for determining the cleavage of the peptide substrates by Hu-Asp2. For example, the specification teaches that in a typical assay, 210 nM enzyme and 200 μM substrate are incubated in 0.2 M sodium acetate at pH 4.5 in 100μl volume at 37°C for 1 to 3 hours. The assay was stopped by the addition of 50 μl 4% TFA to lower the pH below the active range of the enzyme. The results of the reaction are analyzed using an HPLC apparatus equipped with a Vydac column (4.6mm i.d. x 150 mm, 5 □m) pre-equilibrated with 95% A (0.15% TFA in water), 5% B (0.15% TFA in acetonitrile). The cleavage products of the reaction constituents are then eluted from the column using the exemplary elution protocol give at page 41 and the cleavage products are quantitated using an enhanced integrator that quantifies the signal output from the HPLC apparatus. Variations of these assays and elution protocols also are described in the specification.

Applicants respectfully submit that the Examiner's assertions that he cannot ascertain what is cleaved is an inappropriate measure by which to judge the enablement of the claims. The specification teaches how this cleavage of the novel Hu-Asp2 substrates should be effected. One of skill in the art need only follow those teachings and monitor the output of the cleavage assay. Moreover, the claims expressly recite functional language, in that the substrates are defined not only by their sequences but also by their ability to act as substrates for Hu-Asp2. As such, the claim language does not read on non-working embodiments.

The above teachings show that the specification established that it is possible to produce artificial peptides that act as substrates for Hu-Asp2. The specification fully taught how to make such substrates and showed that these peptides act as effective substrates for Hu-Asp2 as determined by the exemplary assay discussed above. As such, the specification provides sufficient objective enablement for making and using the peptides of the present invention commensurate in scope with the claims. Therefore, Applicants respectfully submit that the Examiner's position is untenable in view of the factual teachings of the specification.

The facts of the present case are akin to the facts of *In re Wands*. In that case the court indicated that the sole issue in that case was "whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies." *In re Wands*, 858 F.2d 731, 736. The court specifically noted that no undue experimentation is required to practice an invention if the material being claimed can be made from readily available starting material through routine screening. *Id.* at 739. As a corollary, in the present case the peptides of the present invention are defined by a specific motif which contains a scissile bond that is cleaved by Hu-Asp2, many such peptides are exemplified in the specification. Once the present inventors had taught the specific amino acids residues that should be presented at the scissile bond, those of skill can readily make the peptides of the invention because, much like the technology for making hybridomas that was in question in *In re Wands*, the techniques for generating protein/peptide compositions are well known to those of skill in the art. The mere fact that a large number of peptides (*i.e.*, the ostensibly "millions and millions" referred to by the Examiner) could be generated does not preclude enablement. As the Federal Circuit indicated in Wands, a determination of undue experimentation "cannot be made solely be reference to a particular numerical cutoff." *Id.* at 739, footnote 29. Instead, a determination of what constitutes "undue experimentation" must be made in view of the teachings of the specification when taken in light of what one of skill in the art could do with those teachings at the time the application was filed. Given that the present application has taught the optimization of amino acid residues at positions P_2-P_3' of Hu-Asp2 substrates, one of skill in the art could readily produce such substrates simply by following the teachings of the specification.

Additionally, it is beyond question that the present application provides numerous working examples of peptide substrates of Hu-Asp2. Based on that disclosure it would be a matter of routine experimentation to generate substrates contemplated by the present application. The Court in *In re Wands* went to some lengths to define the term "experiment" as it is used in the monoclonal antibody arts. It stated that "an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody. The process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridoma for the desired characteristics." Id. at 740. There is no credible reason for suggesting that screening a peptide substrate produced in accordance with the teachings the present

invention to determine whether it can be cleaved in an assay, such as the assays specifically described in the specification, would require undue experimentation when the Federal Circuit has clearly admonished that the above screening of numerous hybridomas would not require undue experimentation.

Moreover, in *In re Wands*, the court found that Wands' carrying out the above process three times was sufficient proof of enablement to rebut the Examiner's challenge to the enablement of the disclosure. Here, as can be for example, seen from the data presented in Table 2 (page 20), Table 3 (page 21), Table 4 (page 24), Table 5 (page 25), the Applicants have produced and tested many more than 3 substrates. Applicants submit that in line with the Court's analysis from *In re Wands*, the present application has provided sufficient evidence to effectively rebut the Examiner's challenge to the enablement of the disclosure.

Moreover, Applicants submit that the court has clearly articulated that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970; discussed at MPEP 2164.01(a)). The disclosure of the specific substrates for Hu-Asp2 throughout the specification provides a reasonable correlation to the entire scope of the claimed invention. Further, bearing in mind that the *quid pro quo* for obtaining a patent is to provide an incentive for inventors to disclose their inventions to inure to the benefit of the public, the courts have stated that an '[i]nventor should be allowed to dominate . . . others . . . based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work." (*In re Fisher*, 427 F.2d 833, CCPA 1970). Given that the present inventors were the first to optimize the residues around the cleavage site of the Hu-Asp2 substrate, Applicants contend that the present inventors "should be allowed to dominate others" using the substrate composition claims of the present invention.

In conclusion, given the express working examples that show one of skill in the art how to make and use the peptide compositions of the claimed invention, Applicants submit that the specification conforms to the diktats of *In re Wands*. As discussed above, the

specification provides 1) specific working examples to show one of skill how to set up both assays to determine whether a given peptide would serve as a Hu-Asp2 substrate and the types of results to expect from such assays. These working examples provide 2) the requisite guidance to those skilled in the art of how to test the claimed peptides for desired function. Moreover, 3) the nature of the claimed invention is one in which 4) the level of skill of the ordinary artisan is high. The field of the invention is methods of making protein/peptide compositions, more specifically peptides that serve as substrates for Hu-Asp. Exemplary peptide sequences containing an optimized Hu-Asp2 cleavage region were given in the specification, and 5) the breadth of the claims is such that it is limited to peptides of given structural and functional properties. Finally, Applicants submit that there is 6) a sufficiently high degree of predictability in the field of producing protein variants because recombinant techniques for producing variants of a protein sequence once the amino acid sequence of that protein or the cDNA sequence that encodes that protein is known were common-place and routine at the time the instant application was filed. Therefore, no undue experimentation would be required to produce the claimed peptides.

The above comments directed to claim 21-27 are also applicable to new claims 83-101, inasmuch as these claims incorporate and further narrow the salient features of claim 21. Given the above discussions, Applicants submit that the claimed compositions of the present invention are adequately and objectively enabled, by the specification as filed. As such, Applicants respectfully request withdrawal of the rejection under §112, first paragraph, and reconsideration of the claims for allowance.

V. Rejection under 35 U.S.C. §102(b)/103 should be withdrawn

Claims 21-27 were rejected under 35 U.S.C. §102(b) as allegedly anticipated or alternatively, under 35 U.S.C. §103(a) as obvious over any one of Sermjian *et al.* (*J. Mol. Biol.* 207:1-13, 1989), Van Camp *et al.*, (*Proc. Nat'l. Acad. Sci.*, 87:9903-9907, 1990), Lowell et al., (*J. Biol. Chem.*, 261(18):8442-8452, 1986) or Sellar *et al.*, (*J. Biol. Chem.*, 266(6):3505-3510, 1991). Applicants traverse the rejections and request reconsideration of the claims in light of the comments presented herein below.

Anticipation of a claim requires that the reference teach every element of the claim. MPEP §2131. Thus, "a claim is anticipated only if each and every element as set forth in the

claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 21, its dependent claims 22-27, and new claim 89 are directed to specific peptide substrates of Hu-Asp2 of defined length. It is a specific element of each of these claims that the substrates as claimed are isolated peptides that are between about 4 amino acids and about 50 amino acids in length. None of the references cited by the Examiner disclose an isolated peptide of that length. As such, the references cited cannot properly be said to anticipate the claimed peptides of claims 21-27 or claim 89.

The peptides of new claims 83 to 85 each require that the peptides comprise a label/quenching moiety. Such labels and quenchers are nowhere disclosed in the references cited by the Examiner and therefore these claims also are free of the cited art. New claims 86 to 88 and 90-101 describe peptides longer than 4 amino acids in length and shorter than 50 amino acids in length. For reasons analogous to those presented above, these claims also are not anticipated by the cited art.

In view of the foregoing comments, Applicants respectfully request that the rejection of claims 21-27 under 35 U.S.C. §102(b) be withdrawn.

Moreover, the cited references also do not render obvious the claims of the instant application. In order to render a claimed invention obvious, the cited art not only has to (1) teach or suggest every element of the claimed invention, the cited reference, or combination of references, (2) must also provide some suggestion or motivation to modify the reference(s) to arrive at the claimed invention and (3) there must be some reasonable expectation of the success of such modification of the reference(s). *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). The motivation and the reasonable expectation of success must come from the art and not from the Applicants' own disclosure. As stated in MPEP 2143, all three of the above criteria ***must*** be met in order to properly establish *prima facie* obviousness. It is the Applicants' position that none of these criteria are met by any of the references cited by the Examiner, either individually or in any combination.

In analyzing the claims of the instant application, it should be noted that the claims

are directed to isolated peptide substrates that comprise amino acid lengths of 50 amino acids or shorter. Other claims are directed to peptides that have been modified to permit the detection of cleavage of the peptide by Hu-Asp2. The Examiner asserted that the disclosure of Figure 3 in Semerjian *et al.* may render obvious these claims of the present invention. Applicants respectfully disagree. The entire disclosure of Semerjian *et al.*, is directed to the genetic structure of bacteriophage P22 P_L operon and Figure 3 simply shows the "P22 sequence between *erf* and *sie*B." (see page 7 for description). The sequence highlighted by the Examiner appears to encode a protein that is 103 amino acids in length. There is no indication in the paper that this protein may act as a substrate for Hu-Asp2. There is no suggestion in the reference that one of skill in the art could or should produce fragments of the protein for any purpose, let alone to serve as such substrates. Absent these teaching in the cited art, the peptide substrates of the present invention cannot be rendered obvious by the teachings of Figure 3 of Semerjian et al.

Similarly, the teachings of Van Camp et al., also fail to render obvious the claims of the present application. The Examiner cited Figure 2 of the Van Camp as allegedly defeating the patentability of the present claims. This Figure shows the protein sequence of a superoxide dismutase from *N. plumbaginofolia,* a protein which appears to be 227 amino acids in length. There is no suggestion or motivation anywhere in Van Camp *et al.*, or any other cited reference, that one of skill in the art could or should produce ***peptide fragments*** of this protein that are 4 to 50 amino acids in length. There also is no suggestion for producing such short peptides that have a label or a quenching moiety. One of skill in the art would have no reason to produce such fragments from the teachings of Van Camp *et al.* as there is no teaching or suggestion in that reference of the production of such fragments for use as substrates for Hu-Asp2, or any other purpose. In the absence of these teachings in the art, Van Camp et al. fails to support a *prima facie* case of obviousness of the instantly claimed invention. Lowell et al., also is flawed because the shortest protein sequence taught in Lowell et al. is 75 amino acids in length (see Figure 6.) Thus, a protein substrate of between about 4 to about 50 amino acids in length is not disclosed in Lowell *et al.* Neither the Lowell reference itself, nor any other cited art suggested that it would be desirable to produce fragments of the proteins presented in Figure 6. In addition, the use of any of the proteins of Lowell et al., either full length, or fragments thereof, as Hu-Asp2 substrates is not presented in Lowell et al., or in any other cited document. As such, there is no suggestion in the art to produce the peptide substrates of the present invention.

Moreover, given that there is a complete lack of suggestion to produce peptide substrates of 4 to 50 amino acids in length starting from sequences such as those disclosed in Figure 6, there would be no expectation of success of producing a peptide substrate of the claimed invention. Again, there is no teaching in the cited art that it would be desirable to produce the claimed peptides as substrates for Hu-Asp2, or for any other purpose. Thus, the prior art failed to appreciate that there was any need for such peptides. In the absence of such a teaching, there would be no reason for one of skill in the art to produce such substrates or to expect them to be useful in any Hu-Asp2 related assay. The motivation to produce these substrates and the expectation of success is all derived from the instant specification and not from the prior art. This is an improper premise on which to base an obviousness rejection.

Finally, Sellar *et al.* also fails to provide a disclosure sufficient to render the claimed peptide substrates of the present application obvious. Sellar et al. teaches a dog serum amyloid A (SAA) protein that has multiple isoforms and the amino acid variability between the multiple isoforms. The protein disclosed in the Sellar paper is 129 amino acids in length. There is no suggestion in the Sellar paper that shorter fragments of the protein could or should be produced. Nor is there any suggestion that one of skill in the art use this protein as a basis to design peptide substrates for Hu-Asp2. In the absence of such suggestions in the art, there would be no motivation to produce fragments of the dog SAA isoforms in the Sellar et al. paper to produce the peptide substrates of the present invention.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

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Respectfully submitted,

By _____

Nabeela R. McMillian
Registration No.: 43,363
MARSHALL, GERSTEIN & BORUN
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicants